Case Study: Adaptive Dose Ranging Design

Problem

A dose ranging Phase II trial was designed using basic statistical methods. Four doses of drug were to be included together with placebo. It was calculated that N=84 patients per arm would provide 90% power to detect, for each dose versus placebo, a true delta of 5 units at a 2.5% 1-sided assuming a SD of 10 units. The primary endpoint would be evaluated after 12 weeks treatment.

As an alternative, an adaptive dose ranging design was proposed and evaluated under different dose response profiles.

Design

Rather than randomise N=5x84=420 patients on a 1:1:1:1:1 basis, it was proposed to stage the study as follows:

- In stage 1, initially randomise N=5x28=140 patients and perform an analysis at 12 weeks.
- The results from stage 1 would then be used to guide the randomisation ratio in stage 2. The stage 2 cohort of newly randomised patients would be followed for 12 weeks and a combined analysis of stage 1 and stage 2 patient data performed.
- The results from this combined analysis would then be used to guide the randomisation ratio in stage 3.
- The stage 3 cohort of newly randomised patients would be followed for 12 weeks and a final analysis performed, combining data from all 3 stages.

A rule was defined at the outset that would allow the results at each stage to determine the next stage randomisation ratio; more effective doses being allotted the largest fraction of patients. Also, the design would include a futility criterion, defined at the outset, such that if met by any dose(s) at stage 1 or stage 2, the futile dose(s) would be dropped. Similarly, an extreme efficacy criterion was defined at the outset such that, if met by any dose(s) at stage 1 or stage 2, that dose(s) could be stopped for effectiveness.

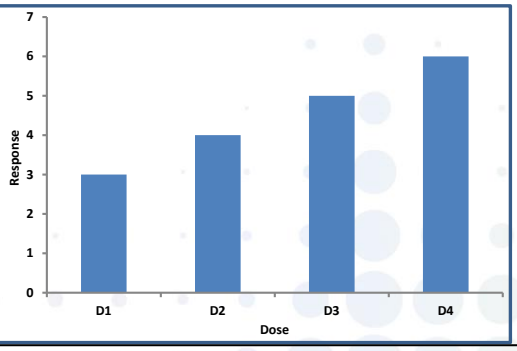
Evaluation

Several possible dose response profiles were evaluated by multiple simulations. The fraction of times a given dose was dropped for futility or stopped for efficacy was assessed and the mean number of patients assigned at each stage and overall calculated together with overall power.

Profile 1:

		1st interim			2nd interim			Final Analysis		
Dose	Rx Effect	n	% drop for futility	% stop for efficacy	n	% drop for futility	% stop for efficacy	n	N	Power
dose1	3	28	19.9%	2.5%	16	25.0%	7.7%	14	58	39.6%
dose2	4	28	10.3%	5.9%	22	12.7%	18.4%	21	71	63.4%
dose3	5	28	5.4%	11.3%	29	6.3%	36.2%	29	86	83.6%
dose4	6	28	2.1%	20.1%	35	2.4%	57.9%	37	100	94.5%

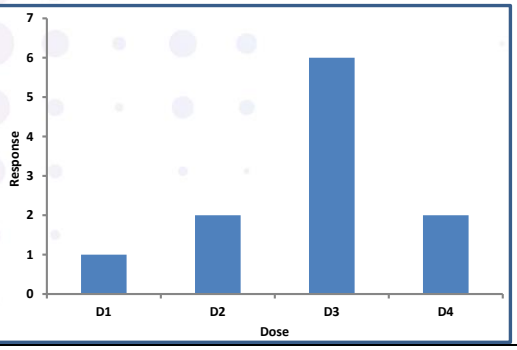
Profile:
Linear Trend Dose response;
Lower doses less effective;
Higher doses better;



Profile 2:

		1st interim			2nd interim			Final Analysis		
Dose	Rx Effect	n	% drop for futility	% stop for efficacy	n	% drop for futility	% stop for efficacy	n	N	Power
dose1	1	28	45.5%	0.3%	9	55.8%	0.8%	7	44	8.0%
dose2	2	28	30.9%	1.2%	14	38.3%	3.0%	12	54	21.1%
dose3	6	28	2.5%	20.6%	44	2.7%	60.7%	48	120	95.3%
dose4	2	28	32.2%	1.1%	14	39.6%	2.7%	12	54	20.7%

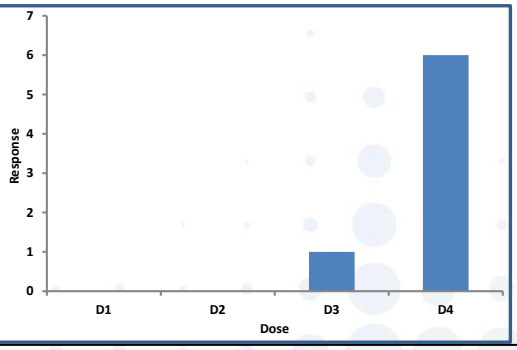
Profile:
Inverted dose response;
Lowest and highest doses less effective; intermediate dose best;



Profile 3:

		1st interim			2nd interim			Final Analysis		
Dose	Rx Effect	n	% drop for futility	% stop for efficacy	n	% drop for futility	% stop for efficacy	n	N	Power
dose1	0	28	59.7%	0.1%	6	71.2%	0.2%	4	38	2.6%
dose2	0	28	59.2%	0.2%	6	70.7%	0.3%	4	38	2.3%
dose3	1	28	45.0%	0.4%	10	55.1%	0.9%	7	45	7.9%
dose4	6	28	2.3%	20.8%	44	2.4%	60.2%	47	119	96.0%

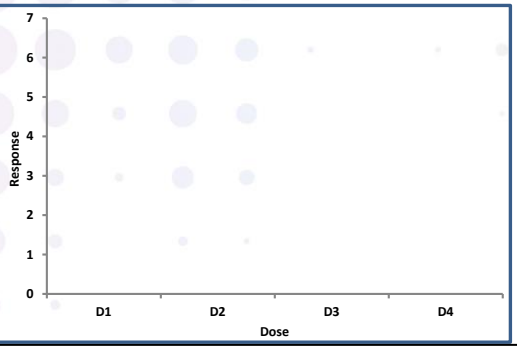
Profile:
Steep dose response;
Lowest doses ineffective;



Profile 4:

		1st interim			2nd interim			Final Analysis		
Dose	Rx Effect	n	% drop for futility	% stop for efficacy	n	% drop for futility	% stop for efficacy	n	N	Type I error
dose1	0	28	60.9%	0.1%	11	72.4%	0.2%	8	47	2.4%
dose2	0	28	60.0%	0.2%	11	72.6%	0.3%	8	47	2.3%
dose3	0	28	59.9%	0.1%	11	72.2%	0.2%	8	48	2.2%
dose4	0	28	59.9%	0.1%	11	72.5%	0.3%	8	47	2.3%

Profile:
All doses ineffective;



Results

Under **Profile 1**, a higher fraction of patients were allocated to the more effective doses such that, at the end of the study, approximately 2x as many patients were allocated to the highest dose than the lowest dose. Lower, less effective doses had an increased chance of being dropped early for lack of efficacy and the higher, more effective doses had

an increased chance of being declared effective earlier in the trial. The average number of patients allocated across the 4 doses was 315, representing a 6% shaving in sample size compared to the original, regular dose response design.

Under **Profile 2**, very few patients were allocated to the lowest, least effective dose and only slightly more were allocated to the marginally more effective doses 2 and 4. These doses had a high chance of being dropped at the first analysis. Dose 3, being the most effective dose, was allocated the majority of patients. The average number of patients allocated across the 4 doses was 272, representing a 20% shaving in sample size compared to the original design.

Under **Profile 3**, doses 1 and 2 were ineffective and consequently carried a high chance of being dropped for futility at the first or second analysis; only an average of 10 additional patients were allocated to these doses over the 28 patients allocated at the outset. Dose 3 which had a small effect was allocated a few more patients but also carried a high chance of being dropped early. Dose 4, which was the clearly effective dose, carried a low chance of being dropped early and was allocated the majority of patients. The average number of patients allocated across the 4 doses was 240, representing a 29% shaving in sample size compared to the original design.

Finally, under the null **Profile 4**, all doses were ineffective. There was a high chance of stopping doses early for inefficacy. The average number of patients allocated across the 4 doses was 189, representing a 44% shaving in sample size compared to the original design. **Importantly, the design parameters laid down at the outset for dropping or stopping doses and for determining the allocation ratio of patients to doses were shown not to inflate the Type I error which was controlled at just under 2.5% 1-sided**.

Conclusion

In the appropriate clinical setting, where the primary endpoint can be evaluated in a reasonably short time frame and given appropriate operational considerations including the ability to quickly turn around results and the use of an Independent Data Monitoring Committee to oversee the staged analyses, an adaptive dose response design will funnel patients toward the more effective doses and, in so doing, can offer efficiencies in trial size particularly when the drug is truly ineffective.

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